

Effects of Pre-Operative Single Dose Gabapentin on Postoperative Pain Following Total Abdominal Hysterectomy: A Dose Finding Study

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How to cite this paper: Kumar, A., Afshan, G. and Naru, T. (2021) Effects of Pre-Operative Single Dose Gabapentin on Postoperative Pain Following Total Abdominal Hysterectomy: A Dose Finding Study. *Open Journal of Anesthesiology*, 11, 279-287.

<https://doi.org/10.4236/ojanes.2021.119027>

Received: May 18, 2021

Accepted: September 25, 2021

Published: September 28, 2021

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Abstract

Background & Aims: The multimodal analgesia provides superior pain relief and reduces opioid consumption and its side effects. Gabapentin has been used successfully in multi-modal analgesia in different doses. We designed a double-blind randomized control trial to find the minimal effective dose of gabapentin in multimodal analgesia for postoperative pain following total abdominal hysterectomy. **Material & Methods:** After informed consent, total of 87 patients were randomly assigned to A, B & C groups to receive gabapentin orally 300 mg, 600 mg, and 900 mg respectively one to two hours before surgery. Postoperatively pain was managed by patient-controlled analgesia (PCA) using pethidine. Pain score, opioid consumption, and side effects of gabapentin were monitored. Rescue analgesia was given and monitored. **Results:** There was no statistically significant difference among the groups with respect to age, weight, height, pethidine consumption, and rescue analgesia. Mean pain scores were statistically insignificant at baseline, 8, 12, and 24 hours postoperatively. Only at 4 hours, the highest pain score (mean) was found in group A, which is statistically significant. The side effects of gabapentin like nausea, vomiting, somnolence, and dizziness were also statistically insignificant. **Conclusion:** A single preoperative oral gabapentin 300 mg was found to be minimal effective dose in multimodal analgesic regimen for reducing post-operative pain and analgesic requirement following total abdominal hysterectomy.

Keywords

PCA, Opioid Effects, Gabapentin, Pethidine, Pain Relief, Total Abdominal Hysterectomy

1. Introduction

Multimodal analgesia is highly recommended in current practice for postoperative pain relief. It provides superior analgesia and reduces opioid consumption & its side effects [1]. Gabapentinoids (gabapentin and pregabalin), newer antiepileptic drugs, are now frequently used in multimodal analgesia for postoperative pain control [2].

Gabapentin has shown promising results in multimodal analgesia. It prevents the release of nociceptive neurotransmitters e.g. glutamate, substance P, and noradrenaline, and decreases postoperative opioid consumption. However, it is associated with some side effects like nausea, dizziness, somnolence, peripheral edema, and lightheadedness [3]. At present, a single minimally effective (optimal) dose of gabapentin is not known in multimodal analgesic regimen using pethidine. The majority of the randomized controlled trials have shown analgesic efficacy of gabapentin with different doses [4] [5]. For orthopedic surgery e.g. total knee and hip replacement, 600 mg of gabapentin 2 hours before surgery decreases postoperative opioid consumption and improves knee range of motion [6]. For breast cancer surgery, the dose of gabapentin from 300 to 1200 mg has been used but the optimal dose of gabapentin is not determined yet [7].

Recent studies on western populations have reported adequate pain relief with gabapentin doses ranging from 300 - 2400 mg per day [8] [9] [10] [11]. There is very limited data available on different doses of gabapentin for postoperative pain relief in our local population. This study aims to find the minimal effective pre-operative dose of gabapentin (considering its significant side effects) in multimodal analgesic regimen for reducing postoperative pain and pethidine requirement following total abdominal hysterectomy.

2. Material and Methods

A prospective, randomized, double-blind trial was conducted at the Aga Khan University Hospital, Karachi for a period of one year after approval from the institutional ethics review committee (ERC). All female patients between 40 to 60 years of age with ASA physical status I to stable III scheduled for total abdominal hysterectomy were included. Exclusion criteria were denial for consent, women with body weight > 85 kg or < 50 kg, with history of epilepsy, vertigo, dizziness, middle ear diseases, allergy, or hypersensitivity to pethidine or gabapentin. Women on sedatives, hypnotics, psychotics, anticonvulsants, and other pain medications used for chronic pain were also excluded.

A total of 87 subjects (29 in each group) were needed to achieve 80% power to detect 10% difference among the groups with a 0.05 significance level. Mean difference was used to calculate sample size by using PASS software (version 11 NCSS, LCC), and 10% mean pethidine consumption difference was considered clinically significant. The mean anticipated pethidine requirement was 600 mg per 24 h (SD = 67.8) [12]. However, the provision of maximum dose of 1680 mg of pethidine/24 hours was available to all study patients using patient-controlled

analgesia (PCA).

After Informed written consent, patients were randomly allocated into 3 groups (29 patients in each group) and were instructed regarding 0 - 10 numerical rating scale (NRS) and operating method of PCA device on preoperative visit. The allocation of patients was done through hospital pharmacy with the centralized computer-generated randomization. Patients received gabapentin 1 - 2 hours before surgery according to the allocated groups *i.e.* 300 mg in group A, 600 mg in group B, and 900 mg in group C. They were pre-medicated by oral midazolam 7.5 mg 1 hour before surgery. Patients and primary investigators (who collected the data) were blinded about the dose of gabapentin given.

General Anaesthesia with control mode of ventilation was given. Induction of anaesthesia was done with propofol (1.5 to 2.0 mg/kg), pethidine (0.8 - 1 mg/kg) & atracurium (0.5 - 0.6 mg/kg) followed by tracheal intubation. Intra-operatively, anaesthesia was maintained with isoflurane and intermittent atracurium. At any time if heart rate and blood pressure were increased to 20% of the baseline and signs of inadequate analgesia were observed then one-third of the induction dose of pethidine was given.

Patients were shifted to post-anaesthesia care unit (PACU) after tracheal extubation and full recovery from anaesthesia. PCA with pethidine was started with settings as per departmental APMS (acute pain management service) protocol 10:10:10 *i.e.* basal infusion: 10 mg/hour, bolus: 10 mg & lockout time: 10 minutes for 24 hours. Pain Assessment was done by numerical rating scale (NRS) at 0 (arrival in the recovery room), 4, 8, 12 and 24 hours postoperatively.

Pethidine consumption was recorded by preserving the total number of demands and goods from PCA device and thereby calculating total consumption of pethidine. Injection morphine 1 - 2 mg I/V stat was given if NRS is 3 - 5 and 2 - 3 mg if NRS is >5 as rescue analgesia in post-operative period. Side effects of gabapentin *i.e.* nausea, vomiting, dizziness, vertigo, and somnolence (when patients report strong desire to sleep during post-operative rounds) were monitored as yes or no scale.

Data was analyzed by Statistical packages for social science version 15 (SPSS Inc., Chicago, IL). Mean and standard deviation were expressed for all quantitative variables like age, weight, height, BMI and pain scores. Categorical variables like somnolence, nausea and vomiting, dizziness and vertigo were reported in frequency and percentage. Chi-square test was applied to compare proportion difference among the groups for side effects while mean difference for quantitative variables was analyzed by analysis of variance (ANOVA). A p-value ≤ 0.05 was considered statistically significant.

3. Results

A total of 87 patients were enrolled and there is no lost to follow up. No statistically significant difference was found among the groups with respect to age, weight, height, and BMI (body mass index) (Table 1).

Table 1. Comparison of demographics among groups.

Variables	Group A n = 29	Group B n = 29	Group C n = 29	p-value
Age (Years)	43.69 ± 5.41	45.66 ± 5.26	45.07 ± 6.52	0.41
Weight (kg)	64.62 ± 12.19	69.07 ± 10.13	66.41 ± 9.63	0.12
Height (cm)	157.09 ± 5.98	155.72 ± 5.50	155.07 ± 4.79	0.65
Body Mass Index (Kg/m ²)	26.14 ± 4.59	28.59 ± 4.68	27.62 ± 3.96	0.11

ANOVA test applied for mean comparison; Results are reported as Mean ± SD.

Comparison of mean pain scores among groups with respect to time *i.e.* at the baseline, 8, 12, and 24 hours postoperatively was statistically insignificant however mean pain scores at 4 hours postoperatively were statistically significant (**Figure 1**). Rescue analgesia was required in 59 patients out of total 87 *i.e.* 67.8%. The group wise calculations are 72.4% (21/29) in group A, 68.9% (20/29) in group B and 62.1% (18/29) patients in group C. Requirement of rescue analgesia *i.e.* mean morphine consumption was not statistically significant (**Figure 2**).

Mean pethidine consumption (240 mg basal infusion plus bolus demands on PCA) among all groups was not statistically significant. (342.93 mg ± 73.61 *i.e.* 43% reduction in group A, 339.31 mg ± 91.17 *i.e.* 44% reduction in group B and 311.9 mg ± 94 *i.e.* 49% reduction in group 3) p = 0.335.

Regarding the side effects of gabapentin, a total of 84 patients out of 87 patients (96.6%) developed somnolence. The group wise calculations are; 28 patients out of 29 (86.6%) in group A, 29 patients out of 29 (100%) in group B and 27 patients out of 29 (93.1%) in group C had somnolence and the difference is not statistically significant (**Table 2**). No statistically significant difference was found for vertigo, dizziness, and nausea/vomiting among three study groups with different doses of gabapentin (**Tables 3-5**).

4. Discussion

The main aim in combining different analgesic drugs is to obtain synergistic or additive analgesia, allowing a smaller dose of each drug with an improved safety profile. Post-operative pain is an important component in the care of surgical patients and is often managed by combinations of opioid and non-opioid medications in multimodal analgesic regimen. The potential role of gabapentin for acute postoperative pain relief has been shown in several randomized clinical trials (RCTs) and it is now considered an important component of multimodal analgesia.

Gabapentin was introduced as an anti-epileptic agent and has been used routinely for treatment of variety of chronic painful conditions. It acts through $\alpha 2\delta$ -subunits of voltage-gated calcium channels and decreases excitatory neurotransmitters, e.g. substance P, glutamate and calcitonin gene-related peptide (CGRP) resulting in overall opioid consumption [13]. Most of the studies/literature

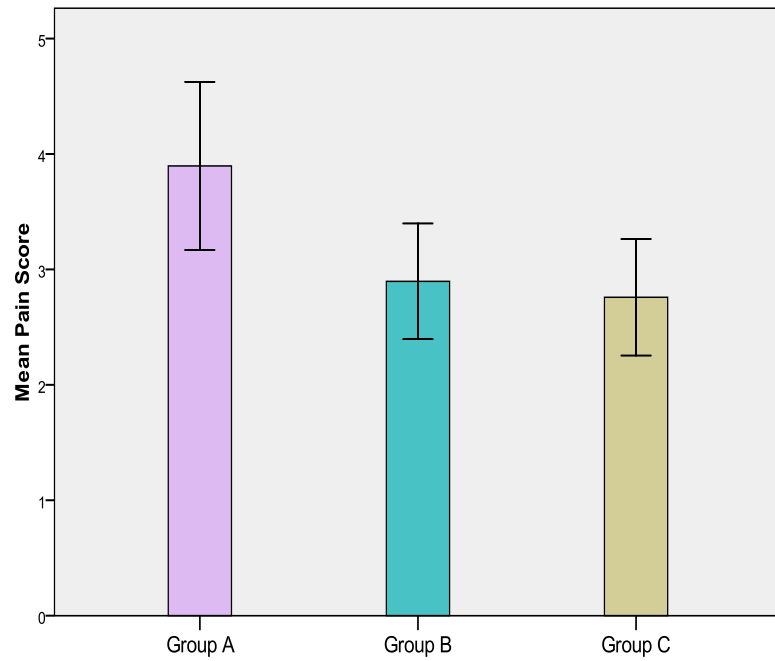


Figure 1. Comparison of mean pain score among groups with respect to time [*significant: Group A vs. B, $p = 0.047$; Group A vs. Group C, $p = 0.019$].

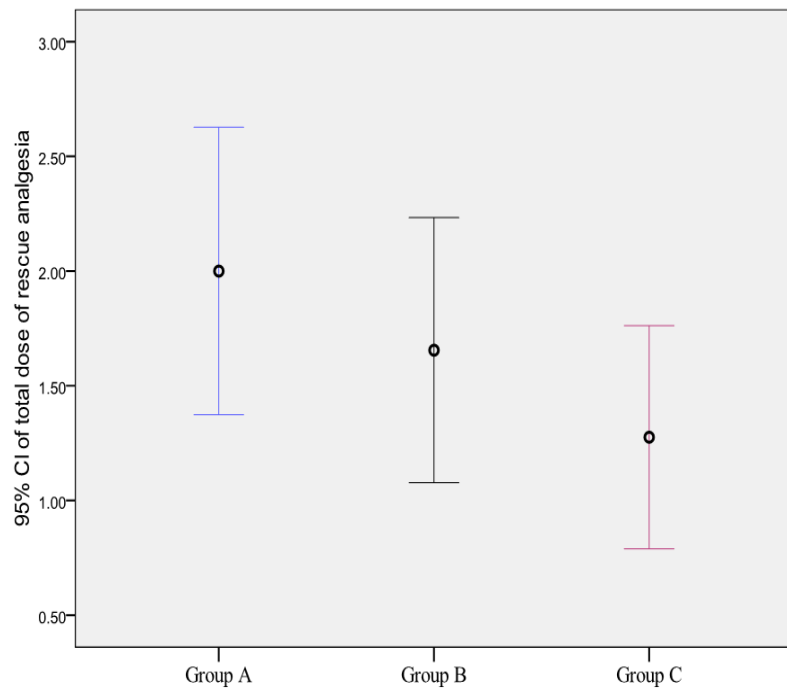


Figure 2. Comparison of total dose rescue analgesia among the groups.

Table 2. Comparison of side effect of somnolence among groups with respect to time.

Somnolence	Patient Groups			p-value
	Group A n = 29	Group B n = 29	Group C n = 29	
At baseline	25 (86.2%)	29 (100%)	26 (89.7%)	0.133
At four hours	22 (75.9%)	26 (89.7%)	23 (79.3%)	0.370
At eight hours	14 (48.3%)	21 (72.4%)	17 (58.6%)	0.171
At twelve hours	11 (37.9%)	11 (37.9%)	7 (24.1%)	0.437
At twenty four hours	2 (6.9%)	2 (6.9%)	1 (3.4%)	0.809

Table 3. Comparison of side effect of vertigo among groups with respect to time.

Vertigo	Patient Groups			p-value
	Group A n = 29	Group B n = 29	Group C n = 29	
At baseline	7 (24.1%)	8 (27.6%)	3 (10.3%)	0.230
At four hours	4 (13.8%)	6 (20.7%)	5 (17.2%)	0.785
At eight hours	7 (21.4%)	3 (10.3%)	5 (17.2%)	0.380
At twelve hours	4 (13.8%)	7 (24.1%)	5 (17.2%)	0.585
At twenty four hours	4 (13.8%)	5 (17.2%)	3 (10.3%)	0.748

Table 4. Comparison of side effect of dizziness among groups with respect to time.

Dizziness	Patient Groups			p-value
	Group A n = 29	Group B n = 29	Group C n = 29	
At baseline	2 (6.9%)	3 (10.3%)	1 (3.4%)	0.584
At four hours	2 (6.9%)	0	0	0.129
At eight hours	2 (6.9%)	1 (3.4%)	0	0.355
At twelve hours	1 (3.4%)	1 (3.4%)	1 (3.4%)	1.0
At twenty four hours	3 (10.3%)	1 (3.4%)	0	0.160

currently available to support the role of gabapentin in reducing opioid consumption is with morphine which is erratically available in Pakistan. We designed this study purposely with pethidine (in equianalgesic dose of morphine) which is available in Pakistan.

Previous studies have shown the effectiveness of gabapentin in different doses but minimal effective dose of gabapentin has not been determined [14]. A recent meta-analysis concluded the dose of preoperative gabapentin from 300 to 1200 mg for postoperative pain relief [7]. However, we did not find any recommendation of gabapentin for post-operative pain relief and reducing pethidine consumption after total abdominal hysterectomy. In this study, we attempted for the minimal effective dose of gabapentin in reducing pethidine consumption. The reason for finding the minimum effective dose is to reduce the side effects of ga-

gabapentin e.g. dizziness, somnolence, and vertigo in postoperative period.

It has been shown in earlier studies that gabapentin significantly decreased morphine consumption and pain scores after mastectomy [15]. Similarly, gabapentin in a total dose of 300 mg in the first 24 hours has shown reduced morphine consumption following total abdominal hysterectomy with no side effects [16].

Pethidine is not recommended as a first choice analgesic by many current guidelines. We believe that if the first choices of opioids are not available, then pethidine can be used in acute pain to ≤ 48 hr and however its dose should not exceed 600 mg/24hr [12]. In this study we found that pethidine consumption is reduced in all three doses of gabapentin *i.e.* 43% in group A, 44% in group B and 49% in group C. Anticipated pethidine dose in our study was 600 mg/24 hour however adding preoperative gabapentin reduced the consumption to nearly 43% - 49%.

The study findings showed that escalating dose of gabapentin does not further decrease pethidine consumption. It is difficult to presume the ceiling effect of 300 mg of gabapentin in multi modal analgesic regimen based on single Centre study. However, future multi-centre large sample size studies can be focused on the ceiling effects of gabapentin on consumption of various opioid.

Sen H *et al.* in their study compared three groups for similar objectives and found that postoperative pain scores were significantly lower in the gabapentin group compared with the ketamine and control groups [17]. In addition, they also found that morphine consumption was significantly reduced in gabapentin and ketamine group (42% and 35% respectively) as compared to control group ($p < 0.001$) [17].

In our study, we used maximum dose of 900 mg and did not find any benefit in terms of reducing pethidine consumption further by increasing the dose from 300 mg. In this study, the side effects associated with gabapentin have been found similar in all groups although we were anticipating more in 900 mg group. This could be due to small sample size of this study or ceiling effects.

Our study has several limitations. The first & foremost is the absence of placebo group. In current practice, gabapentin is highly recommended in acute postoperative pain in multimodal analgesia and using placebo group meant depriving standard of care which poses ethical concerns. A single centre trial and post-operative pain monitoring for 24 hours only are other.

5. Conclusion

A single preoperative oral gabapentin 300 mg was found to be minimal effective dose in multimodal analgesic regimen for post-operative pain relief and reducing pethidine consumption following total abdominal hysterectomy. Further studies are required to investigate the ceiling effect of gabapentin in multi-centered clinical trials.

Acknowledgements

The authors wish to acknowledge Asma Hasnain—Associate, Department of

Anaesthesiology, Aga Khan University for providing assistance in formatting of the manuscript.

Conflicts of Interest

No external funding and no competing interests declared.

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